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PATENT SPECIFICATION (11) 1456618

1456618

(21) Application No. 774/75 (22) Filed 8 Jan. 1975

(31) Convention Application No. 2400819 (32) Filed 9 Jan. 1974 in

(33) Germany (DT)

(44) Complete Specification published 24 Nov. 1976

(51) INT CL² A61K 9/14

(52) Index at acceptance

A5B 753 75Y 764

DTOS

2822882.

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(54) PROCESS FOR THE PRODUCTION OF SOLID PREPARATIONS OF SPARINGLY SOLUBLE MEDICINALLY ACTIVE COMPOUNDS IN A VERY FINELY DIVIDED FORM

(71) We, BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of Leverkusen, Germany, do hereby declare this invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a process for the production of solid preparations of insoluble or sparingly soluble medicinally active substances in a very finely divided form.

Solid medicinally active substances which are insoluble or sparingly soluble in water and/or in gastric and intestinal juice usually have to be converted before incorporation into a solid medicinal preparation, into as finely divided a form as possible to ensure their optimum absorption.

It has been proposed to achieve this by comminuting the medicinally active substances by means of suitable mills. Depending on the nature of the mill, a degree of fineness of from 100 μ to below 5 μ can be achieved. However, this method suffers from the disadvantages that the appropriate, and at times rather costly, grinding facilities have to be available; and that grinding is very time-consuming and causes not inconsiderable nuisance from noise and dust. Furthermore, the degree of fineness achieved is frequently inadequate to give the desired optimum activity.

It has also been proposed to obtain a substantially better degree of fineness by dissolving the medicinally active substance in a special solvent and reprecipitating the medicinally active substance, in a finely divided form, by introducing the solution into, for example, water. The resulting preparation can then be converted into a suspension. Thereafter, for conversion of the suspension into a solid medicinal preparation, the solvent must be removed by suitable drying methods, for example spray drying or roller drying. Though such a method can give medicinal preparations a very fine degree of division, it is very time consuming and cost-intensive.

The present invention provides a relatively simple and inexpensive way of producing a very finely divided product while reducing or avoiding the above disadvantages.

The present invention depends on the surprising discovery that if there is formed a solution of the medicinally active substance in polyethylene glycol in the presence of a surface-active agent the solution can be converted into a dry powder by the addition of sufficient solid inert excipient, which powder on introduction into water releases the active substance in a very finely divided form and hence with excellent bio availability. Rather, it was to be expected that the active compound would separate out from the solvent material onto the excipient in the form of coarse particles and would thus also be released in a coarse form. It seems certain, therefore, that one is dealing here with a solid solution in powder form.

The present invention accordingly provides a process for the production of a finely divided medicinally active preparation which comprises forming a solution of a medicinally active substance in polyethylene glycol in the presence of a surface-active agent, and adding a solid excipient to the solution so as to form a dry powder.

The process according to the invention is especially useful in the formulation of preparations of active substances which are insoluble or sparingly soluble in water and/or gastric and intestinal juice. Examples which may be mentioned here are Clortrimazol, Mefrusid, Nifedipine, Acetylcarbromal, Sulphathiourea, Sulphamethoxydiazine, Niclofolan, Metronidazol, Sulphadiazine, Sulphadimidine, Phenyltoin, Prothionamide, Sulphathiazole, Benzthiazid, Nifurtimox, Sultiam, Niclosamid, 4 - (3' - nitrophenyl) - 2,6 - dimethyl - 1,4 - dihydro - pyridine - 3,5 - dicarboxylic acid bis - (2'' - propoxyethyl) ester and methylphenobarbital.

In carrying out the process according to the invention, a polyethylene glycol with a